

In the specification:

Insert the paper copy of the Sequence Listing filed herewith following the Oath/Declaration.

Replace the paragraph beginning at page 2, line 3 with the following rewritten paragraph:

The flt-1 cDNA (EMBL Accession Number X51602, 7680 bp (SEQ ID No. 25)) encodes a mature protein of 1338 amino acids (SEQ ID No. 26). The structure of the murine flt-1 gene has been determined (Kondo *et al.*, (1998) Gene **208**:297-305) and has been used to predict the intron/exon boundaries within the human gene. The promoter region of the human gene has been characterised (Ikeda *et al.*, (1996) Growth Factors. **13**:151-162; Morishita *et al.*, (1995) J Biol Chem **270**:27948-27953; EMBL Accession Number D64016, 1745 bp (SEQ ID No. 27)). The flt-1 gene, which is organised into thirty exons, has been localised to chromosome 13q12 (Rosnet *et al.* (1993) Oncogene **8**:73-179).

Replace the paragraph beginning at page 2, line 11 with the following rewritten paragraph:

Unless otherwise indicated or apparent from the context, all exon positions herein relate to the positions indicated in EMBL Accession X51602 (SEQ ID No. 25), all promoter positions relate to the positions indicated in EMBL Accession No. 64016 (SEQ ID No. 27), and all intron sequences relate to one or other of SEQ ID Nos 1 - 5 disclosed herein.

Replace the paragraph beginning at page 2, line 15 with the following rewritten paragraph:

SEQ ID No. 1 (1073 bp) represents exon 17 (positions 483 - 615 corresponding to positions 2605-2737 in EMBL Accession No. X51602 (SEQ ID No. 25)) and adjacent intron sequences (positions 1-482 and 616-1073).

Replace the paragraph beginning at page 2, line 18 with the following rewritten paragraph:

SEQ ID No. 2 (1480 bp) represents exon 21 (positions 438 - 594 corresponding to positions 3046-3202 in EMBL Accession No. X51602 (SEQ ID No. 25)), exon 22 (positions 1025-1122 corresponding to positions 3203-3300 in EMBL Accession No. X51602 (SEQ ID No. 25)) and intron sequences adjacent these exons (positions 1-437, 595-1024 and 1123-1480).

Replace the paragraph beginning at page 2, line 22 with the following rewritten paragraph:

SEQ ID No. 3 (726 bp) represents exon 24 (positions 267-278 corresponding to positions 3424-3535 in EMBL Accession No. X51602 (SEQ ID No. 25)) and adjacent intron sequences (positions 1-266 and 279-726).

Replace the paragraph beginning at page 2, line 25 with the following rewritten paragraph:

SEQ ID No. 4 (1352 bp) represents exon 26 (positions 285-390 corresponding to positions 3636-3741 in EMBL Accession No. X51602 (SEQ ID No. 25)), exon 27 (positions 652-794 corresponding to positions 3742-3884 in EMBL Accession No. X51602 (SEQ ID No. 25)) and intron sequences adjacent these exons (positions 1-284, 391-651 and 795-1352).

Replace the paragraph beginning at page 2, line 29 with the following rewritten paragraph:

SEQ ID No. 5 (1256 bp) represents exon 28 (positions 580-664 corresponding to positions 3885-3969 in EMBL Accession No. X51602 (SEQ ID No. 25)) and adjacent intron sequences (positions 1-579 and 665-1256).

Replace the paragraph beginning at page 4, line 31 with the following rewritten paragraph:

The present invention is based on the discovery of nine novel single nucleotide polymorphisms as well as novel intronic sequence of the flt-1 gene. Relative to EMBL Accession No. X51602 (SEQ ID No. 25) the three novel coding sequence polymorphisms are located at nucleotide position: 1953, 3453 and 3888. Relative to EMBL Accession No. D64016 (SEQ ID No. 27) the four novel promoter sequence polymorphisms are located at nucleotide position: 519, 786, 1422 and 1429. Relative to SEQ ID No.3, the intron 24 polymorphism is located at position 454. Relative to SEQ ID No.5, the intron 28 polymorphism is located at position 696.

Replace the paragraph beginning at page 5, line 6 with the following rewritten paragraph:

For the avoidance of doubt the location of each of the polymorphisms (emboldened; published allele (if published) illustrated first) and sequence immediately flanking each polymorphism site is as follows:

Numbering according to EMBL Accession X51602 (SEQ ID No. 25)

a) Position 1953 (codon 568 polymorphism)

GGAAAAAATGCCGACG/AGAAGGAGAGGACCTG (SEQ ID No. 6)  
1938 1968

b) Position 3453 (codon 1068 polymorphism)

GAAATGGATGGCTCCC/TGAATCTATCTTTGAC (SEQ ID No. 7)  
3438 3468

c) Position 3888 (codon 1213 polymorphism)

TGATGATGTCAGATAT/CGTAAATGCTTTCAAG (SEQ ID No. 8)  
3873 3903

Numbering according to EMBL Accession D64016 (SEQ ID No. 27)

d) Position 519 (promoter polymorphism)

AAAAAGACACGGACAC/TGCTCCCCTGGGACCT (SEQ ID No. 9)  
504 534

e) Position 786 (promoter polymorphism)

GATCGGACTTTCCGCC/TCCTAGGGCCAGGCGG (SEQ ID No.10)  
771 801

f) Position 1422 (promoter polymorphism)

GACGGACTCTGGCGGC/TCGGGTCTTTGGCCGC (SEQ ID No. 11)  
1407 1437

g) Position 1429 (promoter polymorphism)

TCTGGCGGCCGGGTCTG/TTTGGCCGCGGGGAGC (SEQ ID No. 12)  
1414 1444

Numbering according to [[Seq]] SEQ ID No. 3 (intron 24)

h) Intron 24 position 454

GAATGTCCTTTGGTTG/AGACAGCCTTTAGATT (SEQ ID No. 13)  
439 469

Numbering according to Seq ID No 5 (intron 28)

i) Intron 28 position 696

AGGTACCTAGTGCACT/CCCGATAGACCCCTTC (SEQ ID No. 14)  
681 711

Replace the paragraph beginning at page 6, line 21 with the following rewritten paragraph:

According to one aspect of the present invention there is provided a method for the diagnosis of one or more single nucleotide polymorphism(s) in *flt-1* gene in a human, which method comprises determining the sequence of the nucleic acid of the human at one or more of positions: 1953, 3453, 3888 (each according to the position in EMBL accession number X51602 (SEQ ID No. 25)), 519, 786, 1422, 1429 (each according to the position in EMBL accession number D64016 (SEQ ID No. 27)), 454 (according to SEQ ID No. 3) and 696 (according to SEQ ID No. 5), and determining the status of the human by reference to polymorphism in the *flt-1* gene.

Replace the paragraph beginning at page 7, line 10 with the following rewritten paragraph:

In one embodiment of the invention preferably the method for diagnosis described herein is one in which the single nucleotide polymorphism at position 1953 (according to the position in EMBL accession number X51602 (SEQ ID No. 25)) is the presence of G and/or A.

Replace the paragraph beginning at page 7, line 13 with the following rewritten paragraph:

In another embodiment of the invention preferably the method for diagnosis described herein is one in which the single nucleotide polymorphism at position 3453 (according to the position in EMBL accession number X51602 (SEQ ID No. 25)) is the presence of C and/or T.

Replace the paragraph beginning at page 7, line 16 with the following rewritten paragraph:

In another embodiment of the invention preferably the method for diagnosis described herein is one in which the single nucleotide polymorphism at position 3888 (according to the position in EMBL accession number X51602 (SEQ ID No. 25)) is the presence of T and/or C.

Replace the paragraph beginning at page 7, line 19 with the following rewritten paragraph:

In another embodiment of the invention preferably the method for diagnosis described herein is one in which the single nucleotide polymorphism at position 519 (according to the position in EMBL accession number D64016 (SEQ ID No. 27)) is the presence of C and/or T.

Replace the paragraph beginning at page 7, line 22 with the following rewritten paragraph:

In another embodiment of the invention preferably the method for diagnosis described herein is one in which the single nucleotide polymorphism at position 786 (according to the position in EMBL accession number D64016 (SEQ ID No. 27)) is the presence of C and/or T.

Replace the paragraph beginning at page 7, line 25 with the following rewritten paragraph:

In another embodiment of the invention preferably the method for diagnosis described herein is one in which the single nucleotide polymorphism at position 1422 (according to the position in EMBL accession number D64016 (SEQ ID No. 27)) is the presence of C and/or T.

Replace the paragraph beginning at page 7, line 28 with the following rewritten paragraph:

In another embodiment of the invention preferably the method for diagnosis described herein is one in which the single nucleotide polymorphism at position 1429 (according to the position in EMBL accession number D64016 (SEQ ID No. 27)) is the presence of G and/or T.

Replace the paragraph beginning at page 8, line 11 with the following rewritten paragraph:

In another aspect of the invention there is provided a method of analysing a nucleic acid, comprising: obtaining a nucleic acid from an individual; and determining the base occupying any one of the following polymorphic sites: 1953, 3453, 3888 (each according to the position in EMBL accession number X51602 (SEQ ID No. 25)), 519, 786, 1422, 1429 (each according to

the position in EMBL accession number D64016 (SEQ ID No. 27)), 454 (according to SEQ ID No. 3) and 696 (according to SEQ ID No. 5).

Replace the paragraph beginning at page 8, line 17 with the following rewritten paragraph:

In another aspect of the invention we provide a method for the diagnosis of flt-1 ligand-mediated disease, which method comprises:

- i) obtaining sample nucleic acid from an individual;
- ii) detecting the presence or absence of a variant nucleotide at one or more of positions: 1953, 3453, 3888 (each according to the position in EMBL accession number X51602 (SEQ ID No. 25)), 519, 786, 1422, 1429 (each according to the position in EMBL accession number D64016 (SEQ ID No. 27)), 454 (according to SEQ ID No. 3) and 696 (according to SEQ ID No. 5), in the flt-1 gene; and,
- iii) determining the status of the individual by reference to polymorphism in the flt-1 gene.

Replace the paragraph beginning at page 8, line 25 with the following rewritten paragraph:

Allelic variation at position 1953 (according to EMBL sequence X51602 (SEQ ID No. 25)) consists of a single base substitution from G (the published base), for example to A. Allelic variation at position 3453 (according to EMBL sequence X51602 (SEQ ID No. 25)) consists of a single base substitution from C (the published base), for example to T. Allelic variation at position 3888 (according to EMBL sequence X51602 (SEQ ID No. 25)) consists of a single base substitution from T (the published base), for example to C. Allelic variation at position 519 (according to EMBL sequence D64016 (SEQ ID No. 27)), consists of a single base substitution from C (the published base), for example to T. Allelic variation at position 786 (according to EMBL sequence D64016 (SEQ ID No. 27)), consists of a single base substitution from C (the published base), for example to T. Allelic variation at position 1422 (according to EMBL sequence D64016 (SEQ ID No. 27)), consists of a single base substitution from C (the published base), for example to T. Allelic variation at position 1429 (according to EMBL sequence D64016 (SEQ ID No. 27)), consists of a single base substitution from G (the published base), for example

to T. Allelic variation at position 454 (according to SEQ ID No. 3) consists of a single base substitution from C to G, for example. Allelic variation at position 696 (according to SEQ ID No. 5) consists of a single base substitution from T to C, for example.

Replace the paragraph beginning at page 13, line 10 with the following rewritten paragraph:

In a further diagnostic aspect of the invention the presence or absence of variant nucleotides is detected by reference to the loss or gain of, optionally engineered, sites recognised by restriction enzymes. For example the polymorphism at position 3888 (numbering according to EMBL sequence X51602 (SEQ ID No. 25)) that alters the third base of codon 1213 can be detected by digestion with the restriction enzyme Sna 1B, as polymorphism at this position creates a Sna 1B recognition sequence (TACGTA).

Replace the paragraph beginning at page 13, line 16 with the following rewritten paragraph:

Engineered sites include those wherein the primer sequences employed to amplify the target sequence participates along with the nucleotide polymorphism to create a restriction site. For example, the polymorphism at position 519 (numbering according to EMBL sequence D64016 (SEQ ID No. 27)) can be detected by diagnostic engineered RFLP digestion with the restriction enzyme Sph 1, since modification of position 516 creates a potential Sph 1 I recognition sequence (GCATGC). Polymorphism at position 519 will modify the recognition sequence (GCAC/TGC).

Replace the paragraph beginning at page 13, line 26 with the following rewritten paragraph:

According to another aspect of the present invention there is provided a nucleic acid comprising any one of the following polymorphisms:  
the nucleic acid disclosed in EMBL Accession Number X51602 (SEQ ID No. 25) with A at position 1953 according to the nucleotide positioning therein;



the nucleic acid sequence disclosed in EMBL Accession Number X51602 (SEQ ID No. 25) with T at position 3453 according to the nucleotide positioning therein;

the nucleic acid sequence disclosed in EMBL Accession Number X51602 (SEQ ID No. 25) with C at position 3888 according to the nucleotide positioning therein;

the nucleic acid sequence disclosed in EMBL Accession Number D64016 (SEQ ID No. 27) with T at position 519 according to the nucleotide positioning therein;

the nucleic acid sequence disclosed in EMBL Accession Number D64016 (SEQ ID No. 27) with T at position 786 according to the nucleotide positioning therein;

the nucleic acid sequence disclosed in EMBL Accession Number D64016 (SEQ ID No. 27) with T at position 1422 according to the nucleotide positioning therein;

the nucleic acid sequence disclosed in EMBL Accession Number D64016 (SEQ ID No. 27) with T at position 1429 according to the nucleotide positioning therein;

the nucleic acid sequence disclosed in SEQ ID No. 3 with G at position 454 according to the nucleotide positioning therein;

the nucleic acid sequence disclosed in SEQ ID No. 3 with A at position 454 according to the nucleotide positioning therein;

the nucleic acid sequence disclosed in SEQ ID No. 5 with T at position 696 according to the nucleotide positioning therein;

the nucleic acid sequence disclosed in SEQ ID No. 5 with C at position 696 according to the nucleotide positioning therein;

or a complementary strand thereof or a fragment thereof of at least 17 bases comprising at least one of the polymorphisms.

Replace the paragraph beginning at page 14, line 21 with the following rewritten paragraph:

According to another aspect of the present invention there is provided an isolated nucleic acid comprising at least 17 consecutive bases of flt-1 gene said nucleic acid comprising one or more of the following polymorphic alleles: A at position 1953 (according to X51602 (SEQ ID No. 25)), T at position 3453 (according to X51602 (SEQ ID No. 25)), C at position 3888 (according to X51602 (SEQ ID No. 25)), T at position 519 (according to D64016 (SEQ ID

No. 27)), T at position 786 (according to D64016 (SEQ ID No. 27)), T at position 1422 (according to D64016 (SEQ ID No. 27)), T at position 1429 (according to D64016 (SEQ ID No. 27)), A at position 454 (according to SEQ ID No. 3) and C at position 696 (according to SEQ ID No. 5), or a complementary strand thereof.

Replace the paragraph beginning at page 15, line 3 with the following rewritten paragraph:

According to another aspect of the present there is provided an allele specific primer capable of detecting an *flt-1* gene polymorphism at one or more of positions: 1953, 3453, 3888 (each according to the position in EMBL accession number X51602 (SEQ ID No. 25)), 519, 786, 1422, 1429 (each according to the position in EMBL accession number D64016 (SEQ ID No. 27)), 454 (according to SEQ ID No. 3) and 696 (according to SEQ ID No. 5).

Replace the paragraph beginning at page 15, line 29 with the following rewritten paragraph:

According to another aspect of the present invention there is provided an allele-specific oligonucleotide probe capable of detecting an *flt-1* gene polymorphism at one or more of positions: 1953, 3453, 3888 (each according to the position in EMBL accession number X51602 (SEQ ID No. 25)), 519, 786, 1422, 1429 (each according to the position in EMBL accession number D64016 (SEQ ID No. 27)), 454 (according to SEQ ID No. 3) and 696 (according to SEQ ID No. 5), in the *flt-1* gene.

Replace the paragraph beginning at page 16, line 25 with the following rewritten paragraph:

In another aspect of the invention, the single nucleotide polymorphisms of this invention may be used as genetic markers for this region in linkage studies. This particularly applies to the polymorphisms at positions 3453, 3888 (both according to the position in EMBL Accession No. X51602 (SEQ ID No. 25)), position 1429 (according to the position in EMBL accession number D64016 (SEQ ID No. 27)), position 454 (according to the position in SEQ ID No. 3) and position 696 (according to the position in SEQ ID No. 5) because of their relatively high

frequency. Those polymorphisms that occur relatively infrequently are useful as markers of low frequency haplotypes.

Replace the paragraph beginning at page 17, line 1 with the following rewritten paragraph:

According to another aspect of the present invention there is provided a method of treating a human in need of treatment with an flt-1 ligand antagonist drug in which the method comprises:

- i) diagnosis of a single nucleotide polymorphism in flt-1 gene in the human, which diagnosis comprises determining the sequence of the nucleic acid at one or more of positions: 1953, 3453, 3888 (each according to the position in EMBL accession number X51602 (SEQ ID No. 25)), 519, 786, 1422, 1429 (each according to the position in EMBL accession number D64016 (SEQ ID No. 27)), 454 (according to SEQ ID No. 3) and 696 (according to SEQ ID No. 5);
- ii) determining the status of the human by reference to polymorphism in the flt-1 gene; and
- iii) administering an effective amount of an flt-1 ligand antagonist drug.

Replace the paragraph beginning at page 17, line 14 with the following rewritten paragraph:

According to another aspect of the present invention there is provided use of an flt-1 ligand antagonist drug in the preparation of a medicament for treating a VEGF-mediated disease in a human diagnosed as having a single nucleotide polymorphism at one or more of positions: 1953, 3453, 3888 (each according to the position in EMBL accession number X51602 (SEQ ID No. 25)), 519, 786, 1422, 1429 (each according to the position in EMBL accession number D64016 (SEQ ID No. 27)), 454 (according to SEQ ID No. 3) and 696 (according to SEQ ID No. 5), in the flt-1 gene.

Replace the paragraph beginning at page 17, line 21 with the following rewritten paragraph:

According to another aspect of the present invention there is provided a pharmaceutical pack comprising an flt-1 ligand antagonist drug and instructions for administration of the drug to

humans diagnostically tested for a single nucleotide polymorphism at one or more of positions: 1953, 3453, 3888 (each according to the position in EMBL accession number X51602 (SEQ ID No. 25)), 519, 786, 1422, 1429 (each according to the position in EMBL accession number D64016 (SEQ ID No. 27)), 454 (according to SEQ ID No. 3) and 696 (according to SEQ ID No. 5), in the flt-1 gene.

Replace the paragraph beginning at page 20, line 24 with the following rewritten paragraph:

In another aspect of the invention there is provided a computer readable medium having stored thereon a nucleic acid sequence comprising at least 20 consecutive bases of the flt-1 gene sequence, which sequence includes at least one of the polymorphisms at positions: 1953, 3453, 3888 (each according to the position in EMBL accession number X51602 (SEQ ID No. 25)), 519, 786, 1422, 1429 (each according to the position in EMBL accession number D64016 (SEQ ID No. 27)), 454 (according to SEQ ID No. 3) and 696 (according to SEQ ID No. 5).

Replace the paragraph beginning at page 21, line 8 with the following rewritten paragraph:

In another aspect of the invention there is provided a method for performing sequence identification, said method comprising the steps of providing a nucleic acid sequence comprising at least 20 consecutive bases of the flt-1 gene sequence, which sequence includes at least one of the polymorphisms at positions: 1953, 3453, 3888 (each according to the position in EMBL accession number X51602 (SEQ ID No. 25)), 519, 786, 1422, 1429 (each according to the position in EMBL accession number D64016 (SEQ ID No. 27)), 454 (according to SEQ ID No. 3) and 696 (according to SEQ ID No. 5) in a computer readable medium; and comparing said nucleic acid sequence to at least one other nucleic acid sequence to identify identity.

Replace the paragraph beginning at page 21, line 16 with the following rewritten paragraph:

In another aspect of the invention there is provided a method for performing sequence identification, said method comprising the steps of providing one or more of the following polymorphism containing nucleic acid sequences:

the nucleic acid disclosed in EMBL Accession Number X51602 (SEQ ID No. 25) with A at position 1953 according to the nucleotide positioning therein;

the nucleic acid sequence disclosed in EMBL Accession Number X51602 (SEQ ID No. 25) with T at position 3453 according to the nucleotide positioning therein;

the nucleic acid sequence disclosed in EMBL Accession Number X51602 (SEQ ID No. 25) with C at position 3888 according to the nucleotide positioning therein;

the nucleic acid sequence disclosed in EMBL Accession Number D64016 (SEQ ID No. 27) with T at position 519 according to the nucleotide positioning therein;

the nucleic acid sequence disclosed in EMBL Accession Number D64016 (SEQ ID No. 27) with T at position 786 according to the nucleotide positioning therein;

the nucleic acid sequence disclosed in EMBL Accession Number D64016 (SEQ ID No. 27) with T at position 1422 according to the nucleotide positioning therein;

the nucleic acid sequence disclosed in EMBL Accession Number D64016 (SEQ ID No. 27) with T at position 1429 according to the nucleotide positioning therein;

the nucleic acid sequence disclosed in SEQ ID No. 3 with G at position 454 according to the nucleotide positioning therein;

the nucleic acid sequence disclosed in SEQ ID No. 3 with A at position 454 according to the nucleotide positioning therein;

the nucleic acid sequence disclosed in SEQ ID No. 5 with T at position 696 according to the nucleotide positioning therein;

the nucleic acid sequence disclosed in SEQ ID No. 5 with C at position 696 according to the nucleotide positioning therein;

or a complementary strand thereof or a fragment thereof of at least 17 bases comprising at least one of the polymorphisms, and comparing said nucleic acid sequence to at least one other nucleic acid or polypeptide sequence to determine identity.

Replace the paragraph beginning at page 23, line 30 with the following rewritten paragraph:

All locations in this section refer to EMBL Accession X51602 (SEQ ID No. 25)  
**EMBL Accession Number X51602 (SEQ ID No. 25), 7680 bp**  
**5' UTR (1-249), Coding (250-4266), 3'UTR (4267-7680)**

Replace the paragraph beginning at page 25, line 9 with the following rewritten paragraph:

All locations in this section refer to EMBL Accession Number D64016 (SEQ ID No. 27)  
**EMBL Accession Number D64016 (SEQ ID No. 27), 1745 bp**  
**Promoter region, exon 1, intron 1**

Product	Forward Primer	Reverse Primer	Temp °C	Time
k. 14-479	14-34	456-479	55	90 sec
l. 343-890	343-366	869-890	55	90 sec
m. 762-1251	762-781	1232-1251	55	90 sec
n. 1151-1694	1151-1172	1673-1694	55	90 sec

Replace the paragraph beginning at page 25, line 25 with the following rewritten paragraph:

**Novel Polymorphisms within coding region - numbering refers to EMBL Accession Number X51602 (SEQ ID No. 25)**

(1)

Position	Polymorphism	Allele Frequency	No of Individuals
1953	G/A	G 90% A 10%	31

Replace the paragraph beginning at page 26, line 6 with the following rewritten paragraph:

**Diagnostic primer (positions 1919-1952 in X51602 (SEQ ID No. 25))**

ATGGGTTTCATGTAACTTGGAAAAATGCG**TAC** (SEQ ID NO: 15)

modified residues in bold underline

**Reverse primer (positions 2098-2125 in X51602 (SEQ ID No. 25))**

CATTCATGATGGTAAGATTAAGAGTGAT (SEQ ID NO: 16)

Replace the paragraph beginning at page 26, line 30 with the following rewritten paragraph:

**Diagnostic primer (Reverse, positions 3487-3454 in X51602 (SEQ ID No. 25), equivalent to positions 330-297 in Seq ID No 3)**

TCTTGGTTGCTGTAGATTTTGTCAAAGATAG**CTGC** (SEQ ID NO: 17)

Modified residues in bold underline

**Forward primer (position 193-216 in Seq ID No 3)**

ACCCCATGGACACTCGGGTTGAAT (SEQ ID NO: 18)

Replace the paragraph beginning at page 27, line 21 with the following rewritten paragraph:

**Forward primer (Positions 362-385 in Seq ID No 5)**

CCTCAACCCTACAGAATGTGAATTG (SEQ ID NO: 19)

**Reverse primer (Positions 828-804 in Seq ID No 5)**

CAGCTAGGTCTAGTTGTCAGTCCTC (SEQ ID NO: 20)

Replace the subtitle beginning at page 28, line 1 with the following rewritten subtitle:  
**Novel polymorphisms within promoter and 5'UTR -numbering refers to EMBL  
Accession Number D64016 (SEQ ID No. 27)**

Replace the paragraph beginning at page 28, line 12 with the following rewritten paragraph:

**Diagnostic primer (Positions 485-518 in D64016 (SEQ ID No. 27))**

GGGTGCATCAATGCGGCCGAAAAAGACACG**G**CA (SEQ ID NO: 21)

Modified residues in bold underline

**Constant primer (Positions 724-741 in D64016 (SEQ ID No. 27))**

GTGTTCTTGGCACGGAGG (SEQ ID NO: 22)

Replace the paragraph beginning at page 28, line 29 with the following rewritten paragraph:

The polymorphism at position 786 can be detected by a diagnostic e RFLP, since modification of position 781,782 creates a NarI recognition sequence (GGCGCC).

Polymorphism at position 786 will modify the recognition sequence (GGCGC**C/T**).

**Diagnostic primer (Positions 751-785 in D64016 (SEQ ID No. 27))**

GGCGCGGCCAGCTTCCCTTGGATCGGACTT**GG**CGC (SEQ ID NO: 23)

Modified residues in bold underline

**Constant primer (Positions 869-890 in D64016 (SEQ ID No. 27))**

Replace the paragraph beginning at page 29, line 17 with the following rewritten paragraph:

Polymorphism at position 1422 alters an EagI recognition sequence (CGGC**T**CG).

**Forward Primer (Positions 1251-1272 in D64016 (SEQ ID No. 27))**

**Reverse primer (Positions 1673-1694 in D64016 (SEQ ID No. 27))**

Replace the paragraph beginning at page 30, line 1 with the following rewritten paragraph:

The polymorphism at position 1429 can be detected by a diagnostic e RFLP, since modification of position 1431,1432 creates a Hinc II recognition sequence (GTTGAC).

Polymorphism at position 1429 will modify the recognition sequence (**G**/TTTGAC).



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**Diagnostic primer (Reverse, positions 1430-1463 in D64016 (SEQ ID No. 27))**

CTGCTCGCCCGGTGCCCCGCGCTCCCCGCGGTTA (SEQ ID NO: 24)

Modified bases in bold underline

**Constant primer (Forward, positions 1251-1272 in D64016 (SEQ ID No. 27))**

Replace the subtitle beginning at page 31, line 6 with the following rewritten subtitle:

**Sequencing Primers (positions refer to Accession X 51602 (SEQ ID No. 25))**